Approach to Glomerular Diseases

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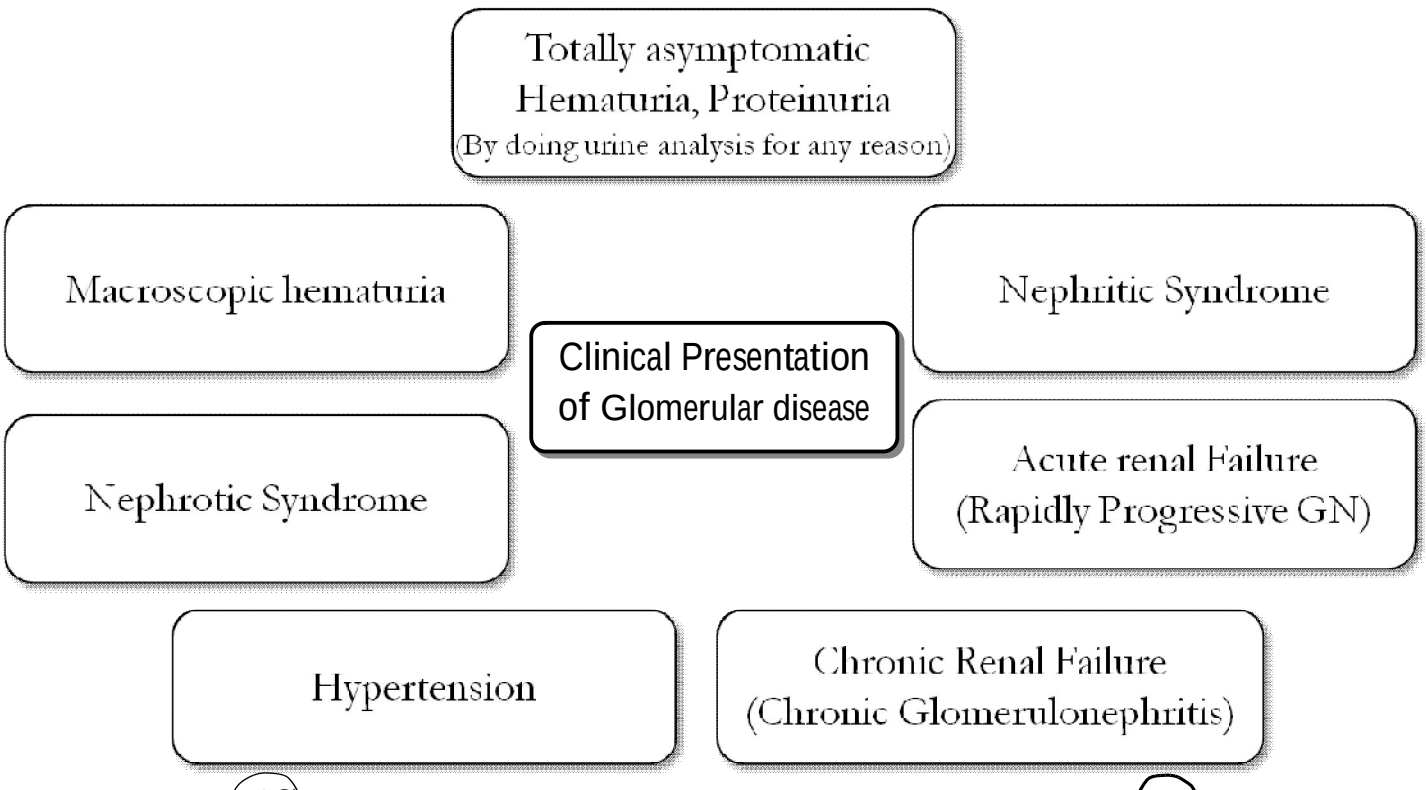
We can clssifying the glomerular diseases into:

- Clinical :
  (more practical)
  - Nephrotic syndrome
  - Nephritic syndrome
    Etc ...

- Pathological classifications :
  (based on kidney biopsy, last thing doing in routine investigation)
  - Minimal changes diseases
  - Membraneous
  - Focal Segmental Glomerulosclerosis
    Etc ...

Clinical Presentation of Glomerular Diseases :



- History: (good history & examination limit your differential diagnosis)
  - Family Hx of kidney disease (Alport's syndrome, Familial)
  - Drugs (NSAID and Antibiotics, **which is nephrotoxic**)
  - Recent of persistent infection (URTI «**such as streptococcus glomrulonephritis**», TB)
  - Malignancies (Lymphoma, breast, etc «may lead to nephrotic or nephritic syndrome»)
  - Multisystem disease:
    - DM **(most common cause to ESRD)**
    - Connective tissue disease **(e.g. SLE)**
    - Vasculitis
- Physical examination :

  Does the pt. have

  - Pitting edema **(bilateral L.L edema)**
  - Periorbital puffiness in morning
  - Edema of gentials and abdominal wall
  - Ascites and pleural effusion **(vol. overload)**
  - Xanthelasma
  - Skin rash **(vascilitis)**
  - Systemic diseases signs (vasculitis, IE, **DM**)
  - Increase BP

- Laboratory studies :

  In order, based on case you started from,

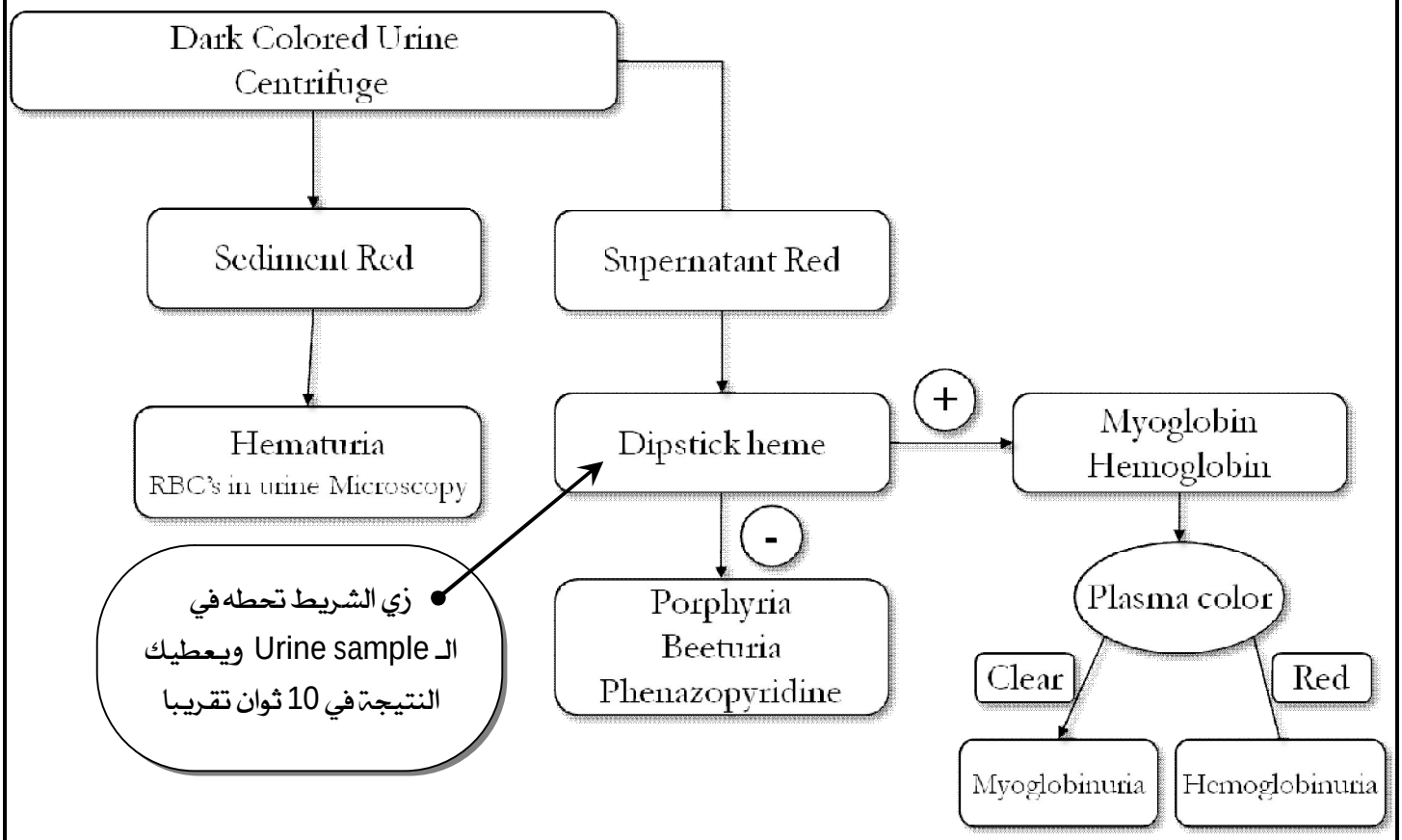
  - Urine analysis
  - 24 h urine protein and creatinine
    - **To know actual amount of protien.**
    - **Now, we used (Protien\Creatinine Ratio) which more convenient.**
    - **Differences in its value may due to differences in the unit.**
  - Serological tests: ANA, Anti-DNA, Hepatitis, ANCA
    - **If you have history of jaundice or blood transfusion, you think about hepatitis.**
    - **If you have rash & arthritis, you're looking for anti-DNA.**
  - Complements level
    - **Helping in classifying GN.**
  - Imaging
    - **Most important is renal US to role out obstruction**
  - Renal Biopsy
    - **The final "gold standard" we're looking to tissue "whole glomerulus" to make diagnosis, but**
    - **We use FNA "fine needle aspiration" in malignancies.**

Approach to Isolated Hematuria :

- Definition :
  - More than 3-5 RBC per high power field microscope in urine.
    - **Not all red urine are hematuria, it may just a concentrate urine.**

- Causes of dark colored urine :
  - Hematuria :
    - **Intact RBC.**
  - Myoglobinuria, Hemoglobinuria :
    - **Hemolysis of blood then excretion of hemoglobien in kidney.**
    - **Not intact RBC.**
  - Porphyria, Beeturia (**common vegetable in north america**), Phenazopyridine
  - Anti-tuberculus drug .
  - Some candies :
    - **Contain high amount of staining ⇒ change colour of urine.**

- Dark Colored Urine :



- Historical Clues for Hematuria :

  - Dysuria **(frequency & urgency it may be UTI especially if she young female)**
  - Renal colic **(have history of stone & flank pain)**
  - Vigorous exercise or trauma **(It cause true hemateuria & rhabdomylsis then myoglonuria)**
  - Bleeding disorders **(sickle cell ⇒ hemolysis ⇒ dark urine)**
  - Cyclic hematuria (contamination or Endometriosis), **(related to menestration)**
  - Medications
  - Systemic disease (SLE **one of commenest disease in our community**, Infective Endocarditis)
  - Recent URTI (IgA **2-3 days** vs. Post-Strept GN **around 2 weeks**)
  - Family history (Alport's syndrome, PCKD, Sickle cell)

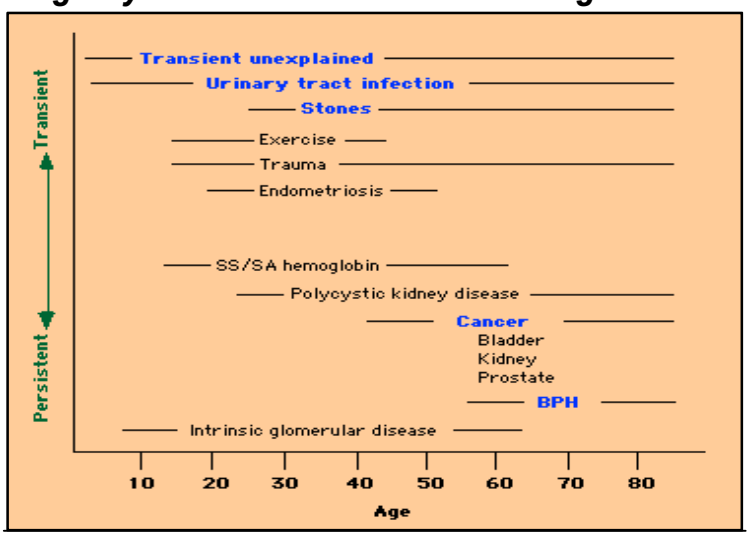
NB

- **Alport's syndrome :**
  - Initially blood in urine then after 10-15 years deterioration of renal function.
- **PCKD :** (Poly Cystic Kidney Disease)
  - Gross hematuria & severe flank pain.

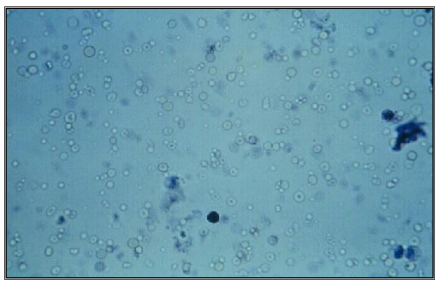
- Causes of Hematuria :

Nephrology	Urology
Glomerular disease: ▪ Reduced in kidney function. ▪ RBC go to tubules by various chemical concentration & it is deformed. ▪ Usually Young: - More likely to have infection	In stone or tumor: ▪ RBC intact. ▪ Examine it by microscope to detect it. ▪ Usually Elderly: - More likely to have tumor

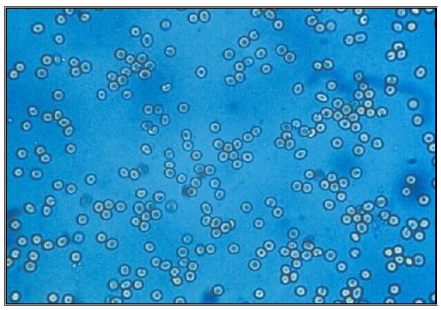
So, history & age will give you a hint to reach correct diagnosis.



» **Glomerular** :
- Causes:
  - IgA
  - Hereditary nephritis
  - Glomerulonephritis :
    - » **Proteinuria**
- Deformed RBC



» **Extra-glomerular :**
- Causes
  - Stones
  - Cysts
  - Malignancy
  - Infarction
- Intact RBC



How to diagnose hematuria ?

» **Exclude Benign Causes** :
- Menstruation **(do not take urine sample during menses)**
- Exercise **(vegourus exercise not mild)**
- Instrumentation (Cystoscopy, Foley Cath**« causeing trauma to urinary tract »**)

» **Role out UTI** :
- Pyuria **(pus in urine)**
- Bacteria, Nitrites
- NOT ISOLATED Hematuria **(we found both RBC & pus in urine)**

» **Role out Anticoagulants** :
- ASA **(Aspirin)**, Coumadin:
  - **We look to INR:**
  - **If INR 2.5 (for e.g.), hematuria is due to tumor because tumor bleed easier than normal tissue. But,**
  - **If INR is 10, then hematuria because of medication.**
- Look for urinary tract disease

- Investigations :
  - Urine analysis
  - Creatinine
  - Ultrasound (helping you to know what r u dealing with)

- Referral of Persistent Hematuria :
  - Exclude benign causes and UTI
  - Nephrologist:
    - Proteinuria
    - New onset HTN
    - Pyuria > 5 cell/HPF
    - Cast (Granular, RBC or WBC) **"aggregate with each other"**
    - Reduced renal function
    - Systemic disease (SLE, HIV, etc)
      - **Skin rash, arthritis, fever ⇒ We're dealing with systemic disease.**
  - Urologist
    - All other cases

» **If there is (Protien+Blood), for sure, it is not urology case but we're dealing with nephrology. "Glomerular disease"**

- Risk factors for bladder cancer :

  - Age:
    - Risk is negligible under 40 years
  - Smoking, past or present
  - Previous urologic tumours
  - Occupational exposure to chemicals or dyes
  - Exposure to certain drugs (e.g.cyclophosphamide)
  - Systemic diseases (e.g. schistosomiasis)
  - History of pelvic radiation

Case I :

- An 18 year-old man is referred for the evaluation of persistent hematuria, detected on a screening medical evaluation. The patient was first noted to have hematuria at the age of 15; no evaluation, however, was performed at that time.
- There is no history of gross hematuria, but the maternal grandfather had renal failure. The urinalysis is notable for microscopic hematuria. BP and Serum creatinine are normal.

So, we're dealing with **nephrology** for many reasons :

- Hematuria for 3 years.
- His grand father had renal failure **unlikely tumor** (because he will die "long time")
- Normal BP & Creatinine does not exclude anything (in early stages)

Case II :

- A 25 year-old women presents with a history of "red urine" and swelling for several days. Physical examination and laboratory analysis are notable for hypertension, periorbital swelling, an elevated plasma creatinine concentration, and red cell casts on urinalysis.

It is **nephrology**:

- Young girl having: red urine, swelling, HTN ...
  - » So, you do not do a favor for her to send her to urology !

Case III:

- A 65 year-old man presents with a history of "red urine" . He is a retired worker in a detergents factory. He use to smoke 20 cigarettes/day, but he quit smoking 3 years ago. Physical examination and laboratory analysis are notable for normal plasma creatinine concentration, and red cells on urinalysis.

It is **urology**:

- He is old , smoker & work with chemical more susceptible for cancer.

- **In conclusion , when we are dealing with hematuria role out the benign cause & then do simple investigation to diagnose the disease.**

Asymptomatic Proteinuria

- Asymptomatic non-nephrotic proteinuria

  - Microalbuminuria :
    - **Earliest clinical manifestation of Diabetic nephropathy.**
    - **It is not only diagnostic, but also prognostic value.**
    - **It carries more risk of cardiovascular**
    - Excretion of 30-150 mg albumin/day
    - Albumin/creatinine (g/g) ratio of 0.03-0.15
    - Used only for diabetic subjects at risk for developing diabetic nephropathy
    - All patients with microalbuminuria should be on ACE-I or ARB
      - **So, control BP is mandatory**

  - Non-Nephrotic :
    - Protein less than 3.5g/24h
      - Urine protein/creatinine ratio < 3
    - Causes:
      - **Glomerular** :
        - » Functional:
          - CHF.
          - Exercise.
          - Fever : **(any fever if you do dipstick , then there are some RBC & it will resolve after treatment)**
          - Orthostatic protienuria : **(protein in urine related with activities during day so, if you do dipstick during day it will be positive & during night will be negative "sleeping time no activity")**
        - » Pathologic: Glomerulonephritis
      - **Tubular** :
        - » Interstitial nephritis
      - **Overflow** :
        - » Multiple myeloma

NB

- If the protein more than 3.5, you do not have to go over all of it, because you are dealing with glomerular disease.
- Nephrotic is glomerulus disease, but
- Non-nephrotic it may be glomerular, tubular & overflow.

- Nephrotic Syndrome :
  (a disease of glumerulus only)

  - Heavy proteinuria (> 3.5 g/d)
  - Hypoalbuminemia (<3.0 g/dL)
  - Generalized edema
  - Hyperlipidemia
    - » **present or absent due to losing protein that help to dissolve the lipid**

⊙ Causes :

- <u>Primary NS</u> :
  - Minimal Change
  - Membraneous
  - FSGS

- <u>Secondary NS</u> :
  - DM
  - SLE
  - Amyloidosis
  - Drugs: Glod, Penecillamine

- It may overlapping e.g. membraneous can be caused by lupus & minimal change can be caused by lymphoma.
- So, we differentiate between them by history. (more older pt more likely to be secondary)

⊙ Complications of Nephrotic Syndrome :

- Negative protein balance due to proteinuria which cause wasting
- Hypercoagulability (DVT, PE, Arterial thrombosis)
  - » **lose the anticoagulants in urine.**
- Hyperlipidemia
- Infections
- Renal failure

Case IV:

- A 22 year-old intravenous drug addict has a four year history of insulin-dependent diabetes mellitus. He is referred for the evaluation of the onset of swelling for one month. Physical examination reveals marked peripheral edema but no retinopathy. Other than a few red cells, microscopic analysis of the urine is unremarkable; the urine total protein to creatinine ratio is 8.0.

It is **nephrotic** secondary to drug addict. (prone to hepatitis & HIV)

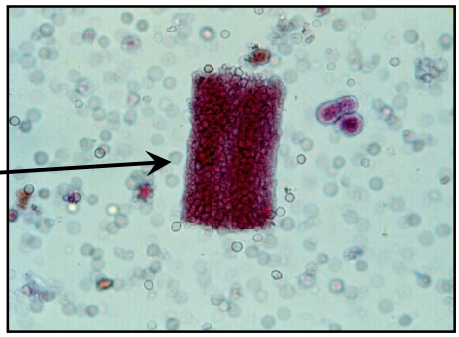
- Unlikely due to DM, because there is no enough time for complication **(Just 4 years)**

Case V :

- A 22 year-old man presents with a several month history of malaise, fatigue, myalgias, and arthralgias. One week ago, he noticed blood-streaked sputum after coughing. Physical examination is unremarkable. Laboratory analysis reveals a plasma creatinine concentration of 186 µmol/L, and numerous red and white cells but no casts are noted on urinalysis.

We are dealing with systemic disease which leading to **nephritic disease**.

- **Nephritic Syndrome :**
  - Acute onset
  - Hematuria (including red cell casts)
  - Mild to moderate proteinuria**, less than nephrotic**
  - Oliguria, hypertension and mild edema



NB

- Post streptococcal GN most common in children, while lupus is the most common in adult.

based on complement we classify nephritic into:

⊙ Nephritic Syndrome - **Low** Serum Complement

- Primary Nephritic Syndrome
  - Post-infectious glomerulonephritis (GN)
  - Membranoproliferative GN - L

- Systemic Nephritic Syndrome
  - Systemic lupus erythematosus (WHO Class III, WHO Class IV) - H
  - Infectious endocarditis
  - HCV-associated cryoglobulinemia

⊙ Nephritic Syndrome - **Normal** Serum Complement

- Primary Nephritic Syndrome
  - IgA Nephropathy
  - Rapidly progressive GN (RPGN), ANCA associated, pauci-immune

- Systemic Nephritic Syndrome
  - Lupus nephritis (WHO Class II) - H
  - Anti-basement membrane disease (Goodpasture's Syndrome) - L
  - Systemic vasculitis:
    - **Polyarteritis nodosa**
    - **Wegener's granulomatosis**
    - **Henoch Schoenlein Purpura**
    - **Thrombotic thrombocytopenic purpura / Hemolytic uremic syndrome**

Differences between Nephritic & Nephrotic syndrome :

Typical features	Nephrotic	Nephritic
Onset	Insidious	Abrupt **(sudden)**
Edema	**++++**	**++**
BP	Normal	Raised
JVP	Normal/ low	Raised
Proteinuria	**++++ (3.5)**	**++**
Hematuria	**+/-**	**+++**
RBC casts	Absent	Present
Serum albumin	Low ↓↓↓	Normal or ↓

Common glomerular diseases presenting as Nephritic Syndrome :

Disease	Association	Helpful test
Post-Strep GN	Pharyngitis Impetigo	ASO titer
Endocarditis Abscess	Murmur	B/C **(blood culture)** Complements
IgA nephropathy	URTI	**After throat infection 2-3 days**
SLE	Symptoms and signs of lupus	ANA, C3,C4

- Acute Renal Failure

  - Pre Renal - Decreased renal perfusion
  - Renal
    - » Rapidly progressive GN (RPGN) :
      - Pauci-immune RPGN, ANCA-associated
      - Anti-glomerular basement membrane disease (Goodpasture)
      - Immune complex mediated RPGN:Systemic lupus erythematosus, IgA Nephropathy , etc …
    - » Acute tubulointerstitial diseases:
      - Acute tubular necrosis (ATN)
      - Acute interstitial nephritis (AIN)
  - Post Renal - Obstruction

- Rapidly Progressive GN

  - Acute severe renal injury with rapid deterioration of renal function over days or weeks

⊙ Clinical presentation:

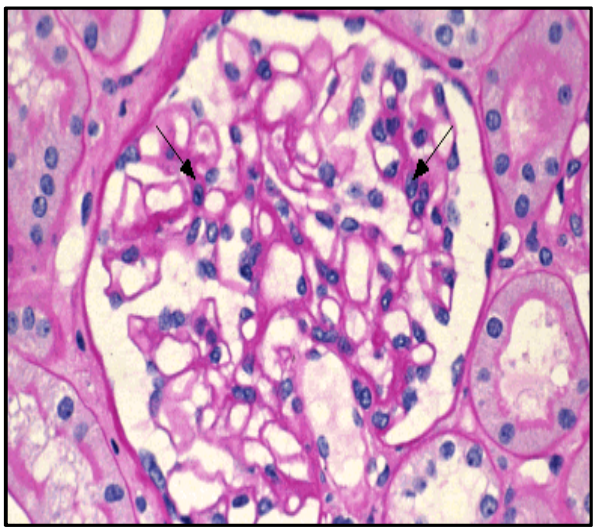
- Uremic symptoms **(nausea , vomiting, ... etc)**
- Severe nephritic syndrome

⊙ Pathology:

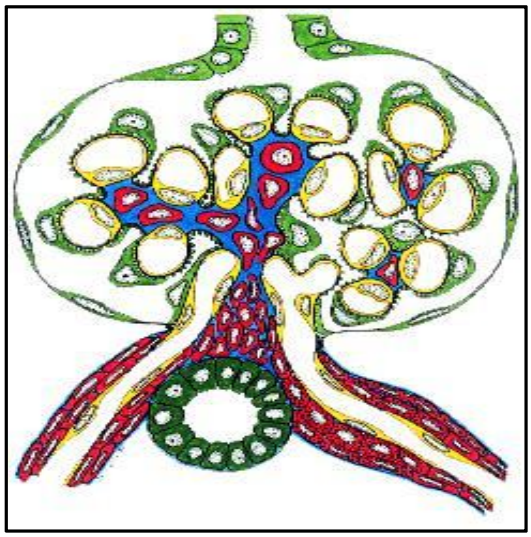
- Indicates rapid destruction (necrosis, fibrosis, etc.) of most of the glomeruli.
- The nephritic syndrome will probably also be present.
- The common denominator is "crescents" present in Bowman's space.

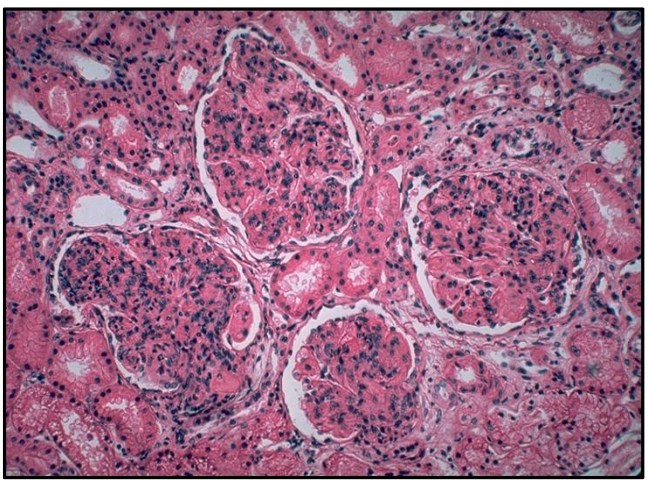
RPGN when pts have hemoptysis, hematiuria & nephritic syndrome
You think of the following :

Disease	Association	Test
Goodpasture's syndrome	Hemoptysis	Anti-GBM Ab
Wegner's	URT involvement	ANCA
Immune complex SLE, Post infectious	Multi-system symptoms	ANA, C3, C4

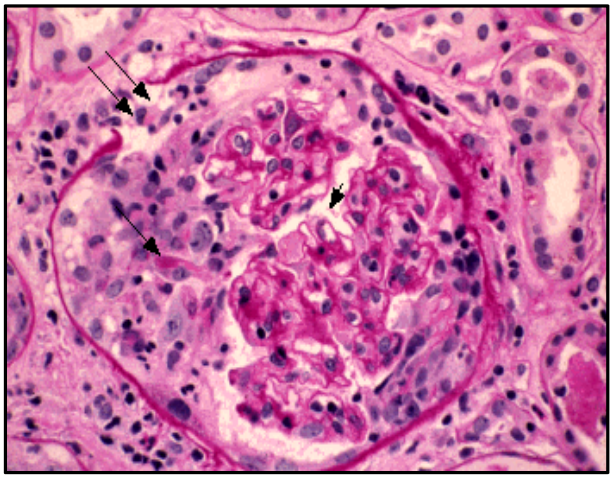


Normal Glomerulous





Rapidly Progressive GN



- Hypertension

⊙ Identifiable Causes of Hypertension

- Sleep apnea
- Drug-induced or related causes
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Steroid therapy and Cushing's syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease

⊙ Laboratory Tests

- Routine Tests
  - Electrocardiogram
  - Urinalysis **& serum cretinine** :
    - **If hematuria & protienuria are present, we are dealing with Glomerular disease causing HTN.**
  - Blood glucose, and hematocrit
  - Serum potassium, creatinine, and calcium
  - Lipid profile
- Optional tests **(based on clinical presentation)** :
  - Measurement of urinary albumin excretion or albumin/creatinine ratio
- More extensive testing for identifiable causes is not generally indicated unless BP control is not achieved

- Non-Specific Treatment of GN :

- **Diuretics, not treat the glomerular disease but to get rid of edema.**
- BP control
- ACE-I/ ARB
- Statin **(lower cholesterol)**
- Low salt and fluid management
- Avoid nephrotoxic drugs
- Diuretics ± Albumin **(if there is no responding to diuretics)**

- Specific Treatment :
  - Steroid
  - Immunosuppressive Drugs
    - Cyclosporin
    - Mycophenolate
    - Cyclophosphamide

NB

- Most common cause of **hematuria in young female** is **UTI** & stone in young male.

Q\ Why glomerulus is commonest site of deposit immuno complx?

- Due to high blood flow to kidney & sometime the stimulus come inside kidney itself by having Ag such in Anti glomerular basement membrane antibodies syndrome.

.: The End :.

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If there is any comments, Please contact us on:

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